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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,357	07/13/2006	Moshe Baru	27048U	1205

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EXAMINER
HA, JULIE

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,357	BARU ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-42,45,47,50,53,54 and 57-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *28-42, 45, 47, 50, 53-54, 57-74* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after non-final office action filed on December 28, 2009 is acknowledged. Claims 28-42, 45, 47, 50, 53-54 and 57-74 are pending in this application. In the previous office action, restriction requirement was withdrawn and all claims have been rejoined. Claims 28-42, 45, 47, 50, 53-54, 57-74 are examined on the merits in this office action.

Withdrawn Rejections

1. Objection to specification due to embedded hyperlink and/or other form of browser-executable code is hereby withdrawn in view of Applicant's amendment to the specification.

2. Objection to claim 65 is hereby withdrawn in view of Applicant's amendment to the claim.

3. Rejection of claim 64 under 35 U.S.C. 112, first paragraph, as failing to comply with written description is hereby withdrawn in view of Applicant's amendment to the claim.

4. Rejection of claims 64, 64 and 67-68 under 35 U.S.C. 102(b) as being anticipated by Allen et al (US Patent No. 5,527,528) is hereby withdrawn in view of Applicant's amendment to the claims.

Maintained Rejections

Rejection-35 U.S.C. 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 28-34, 36-42, 57, 59-60, 62-65, 67-68, 73-74 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Ishikawa et al (US Patent No. 5,824,778) and Igari et al (US Patent No. 5,534,269).

Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles. The particles comprise approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer which carries substantially no net charge. Further, Baru teaches that the protein or polypeptide is capable of externally binding the colloidal particles, or is capable of binding polyethylene glycol and is not encapsulated in the colloidal particle (see abstract). Additionally, the reference teaches these formulations extend the half-life of proteins (see abstract) and the reference teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, binds to membranes comprising phosphatidylcholine:phosphatidylserine (PC:PS) (i.e., two amphipathic lipids); non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V (see p. 7, lines 6-12, claims 18-19), all of which address the limitations of independent claims 28, 57, 59, 64, 73, and 74 and dependent claim 29. The reference teaches that "the term proteins or polypeptides capable of binding polyethylene glycol includes proteins and polypeptides which bind to PEG or derivatives of PEG by any non-covalent mechanism, such as ionic interactions, hydrophobic

interactions, hydrogen bonds and Van der Waals attraction (see p. 7, lines 13-18), meeting the limitation of non-covalent interaction.

The reference further teaches that the colloidal particle has a mean particle diameter of between about 0.05 to about 0.4 microns, and approximately 0.1 microns (see claims 2-3), which meets the limitation of claims 30-31 and 59.

The reference further teaches that the amphipathic lipid is a phospholipid from natural or synthetic sources (see claim 4), which meets the limitation of claims 32 and 36.

The reference teaches the polyethyleneglycol-phosphatidyl ethanolamine (PEG-PE) preparation (see p. 6, lines 19-20), meeting the limitation of claims 33, 60, 62, 63, 65, 67-68, and 74.

Additionally, the reference teaches distearoyl phosphatidyl-ethanoloamine methyl PEG 2000 (DSPE-PEG 2000), meeting the limitation of claim 34.

The reference further teaches that the biocompatible hydrophilic polymer is selected from group consisting of polyalkylether, polylactic and polyglycolic acid families, and is a polyethylene glycol (see claims 6-7), which meets the limitations of claims 39-40.

The reference further teaches that the polyethylene glycol has a molecular weight of between about 1000 to about 5000 daltons (approximately 2000 daltons) (see claims 8-9), which meets the limitations of claims 41-42.

The reference further teaches that “phospholipids used are synthetic and non-toxic, and can therefore, be used in vivo for therapeutic treatment…liposomes do not

encapsulate FVIII, so that smaller sized liposomes can be used which have a longer half-life *in vivo*, since they are not removed by the reticuloendothelial system (RES) (see p. 4, lines 1-6). Since non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V, this meets the limitation of other proteins. The reference teaches the treatment of blood disorder, such as hemophilia (see claim 14). The reference teaches all of the active method steps of instant claim 57. The active method steps of instant claim is that a pharmaceutical composition for parenteral administration is administered to a patient, wherein the protein or polypeptide is not encapsulated in the colloidal particles. The reference teaches administration of a therapeutically effective amount of a compound to a patient in need thereof (see claim 14), and defines that "the term therapeutically effective amount is to be understood as referring to an amount of FVIII which results in a level of FVIII in the bloodstream having a desired therapeutic effect (see p. 4, lines 14-19). The reference further teaches that liposomes containing E-PC/PEG-PE were the most effective since both the initial FVIII activity and the half-life time were higher for this composition than for Kogenate or Kogenate-liposome mixtures where the liposomes were composed of E-PC/PG or E-PC only (see Table 1, p. 11, lines 3-7).

The difference between the reference and the instant claims is that the reference does not teach the protein or polypeptide G-CSF, GM-CSF, and Interferon gamma, which are species required in claim 28, 57, 59, 64, 73, and 74, and does not teach the composition further comprising a second amphipathic lipid of phosphatidylcholine (PC),

as required for Claim 37, or further comprising cholesterol, as required for claims 38 and 73.

Martin et al teach a liposome composition for extended release of a therapeutic compound in to the bloodstream (see abstract). The liposomes are composed of vesicle forming lipids (phospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylinositol (PI) and the like) (see Col. 5, lines 61-66), which teaches limitations of Claim 37. The reference further teaches that the liposomes are between 1-20 mole percent of vesicle-forming lipid derivatized with hydrophilic polymer, having sizes in a selected size range between 0.1 and 0.4 microns, and contain the therapeutic compound in liposome-entrapped form (see abstract). The reference teaches that a biocompatible hydrophilic polymer is PEG having a molecular weight between about 1,000-5,000 daltons, and the polymer is derivatized with the polar head group of phospholipids, such as PE (see Col. 3, lines 1-16 and claims 5 and 6). The reference teaches that these are readily water soluble, can be coupled to vesicle-forming lipids, and are tolerated in vivo without toxic effects (see Col. 5, lines 39-43). The reference further discloses that PEG-liposome has a longer retention time in the blood than the conventional liposomes (see Col. 4, lines 44-46 and Figure 9). The reference teaches that the composition is intended for intravenous administration and the polypeptide may be a peptide or protein, such as superoxide dimutase, **interferons (alpha, beta, and gamma)…colony stimulating factors (M-CSF, G-CSF, GM-CSF)** (see Col. 3, lines 17-41 and claim 9). The reference further teaches supplementation of cholesterol in the composition (see Table 3 and 5), which

teaches the limitation of Claim 38. The reference teaches that cholesterol may be less tightly anchored to a lipid bilayer membrane, particularly when derivatized with a high molecular weight polyalkylether, and therefore be less effective in promoting liposome evasion of the RES in the bloodstream (see Col. 6, lines 3-9). Martin teaches that other lipid components, such as cholesterol, are also known to contribute to membrane rigidity and stability in lipid bilayer structures (see Col. 6, lines 32-35).

Ishikawa et al (US Patent No. '778) teaches that "it has been desired to prolong the half-life of human G-CSF in the body as to enhance it s effects, as may be expected. Improvement in biological activity and pharmacokinetics, which may be expected as a result of the modification of human G-CSF by polyethylene glycol is described (see column 1, lines 55-63). Furthermore, Igari et al (US Patent No. '269) teaches that "thanks to advances in genetic engineering and cell engineering technologies, some (proteins) have been produced in large mounts for pharmaceutical application…Such protein pharmaceuticals include interferons (alpha, beta, gamma)...erythropoietin and granulocyte colony-stimulating factor (G-CSF). These proteins, however, since they have generally short biological half-life, must be administered frequently, posing the significant physical burden of injection on patients. To solve this problem, various attempts have been made to develop sustained-release preparations" (see column 1, lines 11-29).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru and Martin, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount

of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V of and Martin et al teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes. Both Ishikawa and Igari teach that protein pharmaceuticals are known to have short half life, including G-CSF, interferon Gamma and other proteins, and various attempts have been developed to develop sustained-release preparation. Therefore, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. One of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life *in vivo***, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated in vivo without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). Furthermore, pegylation of protein is general concept in the protein arts (see Ishikawa). PEGylcation of proteins increases half-life of these proteins, including G-CSF, interferon gamma and factor VIII (including

prothrombin, factor X and so on disclosed in Baru reference). There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

Response to Applicant's Arguments

7. Applicant argues that "a proper case of prima facie obviousness has not been established because the combination of Baru with Martin is improper because there is no suggestion or motivation to combine the reference teachings or to modify the reference." Applicant further argues that "the proteins or polypeptides of Baru are not encapsulated in the colloidal particles. Martin, on the other hand, describes liposome compositions which 'contain the therapeutic compound in liposome-entrapped form'. The skilled artisan would not combine these references since they teach liposome compositions of significantly different structure, one in which the protein is outside the liposome and one in which the protein is inside the liposome...the skilled artisan when reviewing Martin that describes encapsulate proteins, would have not motivation to look to art describing liposomes where the protein is not encapsulated." Applicant further argues that "although Baru discloses the coagulation factors Factor VIII, prothrombin,

Factor X and Factor V, this does not make obvious the use of Factor VIIa...these factors have completely different physico-chemical properties. It is these properties, and not the therapeutic use, which determine whether the protein will be active when bound to the colloidal particle, and whether the half life will be extended." Applicant further argues that "Martin teaches away from using cholesterol." Furthermore, Applicant argues that "Ishikawa and Igari merely teach that G-CSF has a short biological half life, but do not teach how this problem may be overcome."

8. Applicant's arguments have been fully considered but have not been found persuasive. As indicated by the rejection above, the difference between the reference and the instant claim is that the reference does not teach the protein or polypeptide G-CSF, GM-CSF, and Interferon gamma. Since the rejection is based on the protein or polypeptide G-CSF, GM-CSF, and Interferon gamma, Applicant's arguments regarding Factor VIIa is moot. Motivation of the instant rejection was to add G-CSF, GM-CSF and Interferon gamma since the prior arts teach that these have short half lives. Applicant argues that the references do not "make obvious the use of factor VIIa." It is unclear how this is relevant to substituting the other coagulation factors taught in Baru with G-CSF, GM-CSF and Interferon gamma. Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles. Additionally, Baru teaches that these formulations extend the half-life of proteins and the reference teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, binds to membranes

comprising phosphatidylcholine:phosphatidylserine (PC:PS) (i.e., two amphipathic lipids); non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al teach a liposome composition for extended release of a therapeutic compound in to the bloodstream. Martin reference teaches that the liposomes are composed of vesicle forming lipids (phospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylinositol (PI) and the like) and further teaches that the liposomes are between 1-20 mole percent of vesicle-forming lipid derivatized with hydrophilic polymer, having sizes in a selected size range between 0.1 and 0.4 microns, and contain the therapeutic compound in liposome-entrapped form. The mere fact that one is entrapped would not negate the reasonable expectation of success. Baru reference showed that proteins or polypeptide externally binding the colloidal particles, and Martin reference showed that protein or polypeptides encompassed within the same colloidal particle. Both references teach that the half-life of the protein or polypeptides can be extended. Furthermore, Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life *in vivo***, because they are not removed by the RES.

In regards to Applicant's argument that "although Baru discloses the coagulation factors Factor VIII, prothrombin, Factor X and Factor V, this does not make obvious the use of Factor VIIa...these factors have completely different physico-chemical properties," Baru teaches the same family of proteins, coagulation factors Factor VIII, prothrombin, Factor X and Factor V. Again, the rejection is based on the other proteins

G-CSF, GM-CSF and Interferon gamma, and not to Factor VIIa. This argument has no relevance in the instant rejection.

In regards to "different physico-chemical properties" physico-chemical properties have no bearing on reason to modify. Furthermore, as Applicant indicates at page 9 of remarks page, Factor VIII has MW of 330,000; prothrombin has MW of 72,000. Factor X has MW of 58,500. Factor V has MW of 330,000; Factor VIIa has MW of 50,0000. For example, Factor X is a protein having 482 amino acids; Factor VIII is a protein having 2319 amino acids; Factor V is a protein having 2206 amino acids. Given the different size and sequence of each of coagulation factors taught in Baru, one would expect these to have different physiochemical properties from one another. Yet, Baru reference teaches that different sized proteins can bind externally to the colloidal particle, and the half-life of the protein is extended. Given the variation of protein sizes taught by Baru reference, any size protein would work; size is not relevant. Further, Factor VIIa has close MW to Factor X. One would expect Factor VIIa to have the same effect as Factor X. In regards to “Martin reference teaches away from using cholesterol,” Martin teaches that other lipid components, such as cholesterol, are also known to contribute to membrane rigidity and stability in lipid bilayer structures. Therefore, one would be motivated to add the cholesterol to increase the stability in lipid bilayer structures. Therefore, Martin reference does not teach away from using cholesterol.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru and Martin, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount

of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V and Martin et al teach Interferon gamma, G-CSF, GM-CSF, and other protein that are incorporated with the liposomes. Since one worked for entrapped within colloidal particle (Martin) and one worked for binding externally to the colloidal particle (Baru), one would expect that both would work the same way. Furthermore, both Ishikawa and Igari teach that protein pharmaceuticals are known to have short half life, including G-CSF, interferon Gamma and other proteins, and various attempts have been developed to develop sustained-release preparation. Therefore, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. One of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life *in vivo***, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated in vivo without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). There is a

reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

9. Claims 28-34, 36-42, 57, 59-60, 62-65, 67-68, 73-74 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Chen et al (US Patent No. 5,512,549) or Galloway et al (US Patent No. 5,705,483).

The teachings of Baru and Martins are described, *supra*. The difference between the references and the instant claims is that the references do not teach GLP-1.

However, Chen et al teach that “presently, therapy involving the use of GLP-1 type molecules has presented a significant problem because the serum half-life of such peptides is quite short. For example, GLP-1(7-37) has a serum half-life of only 3 to 5 minutes. Presently, the activity of dipeptidyl-peptidase IV (DPP IV) is believed to readily inactivate GLP-1(7-37) in addition to rapid absorption and clearance following parenteral administration. Thus, there exists a critical need for biologically active GLP-1 (7-37) analogs that possess extended pharmacodynamic profiles following parenteral administration" (see column 3, lines 13-22). Galloway also teaches that “the biological

half-life of GLP-1 molecules, particularly those molecules which are affected by the activity of dipeptidyl-peptidase IV (DPP IV) is quite short. For example, the biological half life of GLP-1 (7-37) is a mere 3 to 5 minutes (see column 3, lines 41-45), and is further influenced by its rapid absorption following parenteral administration to a mammal. Thus, there also exists a need for a GLP-1 compound which delays absorption following administration" (see column 3, lines 41-48).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al, Martins et al patents, Chen et al or Galloway et al, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes.

Furthermore, Chen and Galloway both teach that "there exists a need for a GLP-1 compound that possess extended pharmacodynamic profile (increased half-life) following parenteral administration." Therefore, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing

PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life *in vivo***, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated *in vivo* without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). PEGylation of proteins increases half-life of these proteins, including G-CSF, interferon gamma and factor VIII (including prothrombin, factor X and so on disclosed in Baru reference) and GLP-1. There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

Response to Applicant's Arguments

10. Applicant argues that "a proper case of prima facie obviousness has not been established because the combination of Baru with Martin is improper because there is no suggestion or motivation to combine the reference teachings or to modify the

reference." Applicant further argues that "the proteins or polypeptides of Baru are not encapsulated in the colloidal particles. Martin, on the other hand, describes liposome compositions which 'contain the therapeutic compound in liposome-entrapped form'. The skilled artisan would not combine these references since they teach liposome compositions of significantly different structure, one in which the protein is outside the liposome and one in which the protein is inside the liposome...the skilled artisan when reviewing Martin that describes encapsulate proteins, would have not motivation to look to art describing liposomes where the protein is not encapsulated." Applicant further argues that "although Baru discloses the coagulation factors Factor VIII, prothrombin, Factor X and Factor V, this does not make obvious the use of Factor VIIa...these factors have completely different physico-chemical properties. It is these properties, and not the therapeutic use, which determine whether the protein will be active when bound to the colloidal particle, and whether the half life will be extended." Applicant further argues that "Martin teaches away from using cholesterol." Furthermore, Applicant argues that "Chen and Galloway merely teach that GLP-1 has a short biological half life, but do not teach how this problem may be overcome."

11. Applicant's arguments have been fully considered but have not been found persuasive. As indicated by the rejection above, the difference between the reference and the instant claim is that the reference does not teach GLP-1. Since the rejection is based on GLP-1, Applicant's argument regarding Factor VIIa is moot. Motivation of the instant rejection was to add GLP-1 since the prior arts teach that these have short half lives. Applicant argues that the references do not "make obvious the use of factor VIIa."

It is unclear how this is relevant to substituting the other coagulation factors taught in Baru with GLP-1. Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles. Additionally, Baru teaches that these formulations extend the half-life of proteins and the reference teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, binds to membranes comprising phosphatidylcholine:phosphatidylserine (PC:PS) (i.e., two amphipathic lipids); non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al teach a liposome composition for extended release of a therapeutic compound in to the bloodstream. Martin reference teaches that the liposomes are composed of vesicle forming lipids (phospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylinositol (PI) and the like) and further teaches that the liposomes are between 1-20 mole percent of vesicle-forming lipid derivatized with hydrophilic polymer, having sizes in a selected size range between 0.1 and 0.4 microns, and contain the therapeutic compound in liposome-entrapped form. The mere fact that one is entrapped would not negate the reasonable expectation of success. Baru reference showed that proteins or polypeptide externally binding the colloidal particles, and Martin reference showed that protein or polypeptides encompassed within the same colloidal particle. Both references teach that the half-life of the protein or polypeptides can be extended. Furthermore, Baru reference teaches that when the liposomes do not encapsulate the

therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life *in vivo***, because they are not removed by the RES.

In regards to Applicant's argument that "although Baru discloses the coagulation factors Factor VIII, prothrombin, Factor X and Factor V, this does not make obvious the use of Factor VIIa...these factors have completely different physico-chemical properties," Baru teaches the same family of proteins, coagulation factors Factor VIII, prothrombin, Factor X and Factor V. Again, the rejection is based on GLP-1, and not to Factor VIIa. This argument has no relevance in the instant rejection.

In regards to "different physico-chemical properties" physico-chemical properties have no bearing on reason to modify. Furthermore, as Applicant indicates, Factor VIII has MW of 330,000; prothrombin has MW of 72,000. Factor X has MW of 58,500. Factor V has MW of 330,000; Factor VIIa has MW of 50,0000. For example, Factor X is a protein having 482 amino acids; Factor VIII is a protein having 2319 amino acids; Factor V is a protein having 2206 amino acids. Given the different size and sequence of each of coagulation factors taught in Baru, one would expect these to have different physiochemical properties from one another. Yet, Baru reference teaches that different sized proteins can bind externally to the colloidal particle, and the half-life of the protein is extended. Given the variation of protein sizes taught by Baru reference, any size protein would work; size is not relevant. Further, Factor VIIa has close MW to Factor X. One would expect Factor VIIa to have the same effect as Factor X. In regards to "Martin reference teaches away from using cholesterol," Martin teaches that other lipid components, such as cholesterol, are also known to contribute to membrane rigidity and

stability in lipid bilayer structures. Therefore, one would be motivated to add the cholesterol to increase the stability in lipid bilayer structures. Therefore, Martin reference does not teach away from using cholesterol.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru and Martin, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V and Martin et al teach Interferon gamma, G-CSF, GM-CSF, and other protein that are incorporated with the liposomes. Since one worked for entrapped within colloidal particle (Martin) and one worked for binding externally to the colloidal particle (Baru), one would expect that both would work the same way. Furthermore, Chen and Galloway both teach that "there exists a need for a GLP-1 compound that possess extended pharmacodynamic profile (increased half-life) following parenteral administration." Therefore, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. One of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer**

half-life *in vivo*, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated in vivo without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

12. Claims 28-34, 36-42, 47, 50, 53, 57, 59-60, 62-65, 67-68, 73-74 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Heldman et al (US 2006/0039962 A1, 102(e) date) as evidenced by (http://www.copaxone.com/, prescribing information, accessed 7/27/2009) and further in view of Braxton SM (US Patent No. 5,766,897).

The teachings of Baru and Martin et al is described, *supra*. The difference between the references and the instant claims is that the reference does not teach Copaxone® and treatment of MS.

However, Heldman et al teach amphiphilic compound capable of forming vesicles or liposomes (see abstract). The reference teaches that the vesicle preparations are designed for delivering therapeutic agents which have a short lifetime at the delivery sites (e.g. stomach, intestine, etc) and have to be released at the site of action in another part of the body...insulin for the treatment of diabetes, or Cop 1 (Copaxone®) for the treatment of multiple sclerosis, or antibodies such as Herceptin for the treatment of breast cancer (see paragraph [0224], and claims 39-40). Braxton patent No. '897 teaches exemplary proteins for which an increase half-life has been accomplished by PEGylation of the protein include: hGH, **insulin**, interferon, tPA, **EPO, G-CSF…factor VIII…IgG** and so on (see column 25, lines 9-38).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al, Martins et al patents, Heldman et al and Braxton patent, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al teach

Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes.

Furthermore, Heldman et al teach that Copaxone®, insulin, herceptin (monoclonal antibody) all have very short lifetime at the delivery site. As evidenced by www.copaxone.com, multiple sclerosis (MS) is known to be treatable by Copaxone®. Therefore, it would have been obvious to one of ordinary skill in the art to treat multiple sclerosis with a pharmaceutical composition comprising Copaxone® non-covalently bound to colloidal particle. Further, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life *in vivo***, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated *in vivo* without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). PEGylation of proteins increases half-life of these proteins, including G-CSF, interferon gamma and factor VIII (including prothrombin, factor X and so on disclosed in Baru reference), insulin, Copaxone® and antibodies (Heldman and Braxton). There is a reasonable

expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

Response to Applicant's Arguments

13. Applicant argues that "a proper case of prima facie obviousness has not been established because the combination of Baru with Martin is improper because there is no suggestion or motivation to combine the reference teachings or to modify the reference." Applicant further argues that "the proteins or polypeptides of Baru are not encapsulated in the colloidal particles. Martin, on the other hand, describes liposome compositions which 'contain the therapeutic compound in liposome-entrapped form'. The skilled artisan would not combine these references since they teach liposome compositions of significantly different structure, one in which the protein is outside the liposome and one in which the protein is inside the liposome...the skilled artisan when reviewing Martin that describes encapsulate proteins, would have not motivation to look to art describing liposomes where the protein is not encapsulated." Applicant further argues that "although Baru discloses the coagulation factors Factor VIII, prothrombin, Factor X and Factor V, this does not make obvious the use of Factor VIIa...these factors

have completely different physico-chemical properties. It is these properties, and not the therapeutic use, which determine whether the protein will be active when bound to the colloidal particle, and whether the half life will be extended." Applicant further argues that "Martin teaches away from using cholesterol." Furthermore, Applicant argues that "Heldman describes vesicles and liposomes made from amphiphilic derivatives for site-directed delivery of therapeutic agents…the vesicles and liposomes can be used for encapsulating drugs and delivering them." Applicant argues that "the liposomes of Heldman have a completely different lipid component...the liposomes of Heldman have no amphipathic lipid derivatized with a biocompatible hydrophilic polymer." Applicant argues that "internet citation is cited as teaching that MS is treatable with COPAXONE®. Nothing is taught regarding how to extend the biological half life of COPAXONE®." Further, Applicant argues that "Braxton describes that PEGylation of certain proteins increases their half lives. Braxton does not teach or allude to the presently claimed composition."

14. Applicant's arguments have been fully considered but have not been found persuasive. As indicated by the rejection above, the difference between the reference and the instant claim is that the reference does not teach COPAXONE® and the treatment of MS. Since the rejection is based on COPAXONE®, Applicant's argument regarding Factor VIIa is moot. Motivation of the instant rejection was to add COPAXONE® since the prior art teaches that COPAXONE® has short half life. Applicant argues that the references do not "make obvious the use of factor VIIa." It is unclear how this is relevant to substituting the other coagulation factors taught in Baru

with COPAXONE®. Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles. Additionally, Baru teaches that these formulations extend the half-life of proteins and the reference teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, binds to membranes comprising phosphatidylcholine:phosphatidylserine (PC:PS) (i.e., two amphipathic lipids); non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al teach a liposome composition for extended release of a therapeutic compound in to the bloodstream. Martin reference teaches that the liposomes are composed of vesicle forming lipids (phospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylinositol (PI) and the like) and further teaches that the liposomes are between 1-20 mole percent of vesicle-forming lipid derivatized with hydrophilic polymer, having sizes in a selected size range between 0.1 and 0.4 microns, and contain the therapeutic compound in liposome-entrapped form. The mere fact that one is entrapped would not negate the reasonable expectation of success. Baru reference showed that proteins or polypeptide externally binding the colloidal particles, and Martin reference showed that protein or polypeptides encompassed within the same colloidal particle. Both references teach that the half-life of the protein or polypeptides can be extended. Furthermore, Baru reference teaches that when the liposomes do not encapsulate the

therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life *in vivo***, because they are not removed by the RES.

In regards to Applicant's argument that "although Baru discloses the coagulation factors Factor VIII, prothrombin, Factor X and Factor V, this does not make obvious the use of Factor VIIa...these factors have completely different physico-chemical properties," Baru teaches the same family of proteins, coagulation factors Factor VIII, prothrombin, Factor X and Factor V. Again, the rejection is based on COPAXONE®, and not to Factor VIIa. This argument has no relevance in the instant rejection.

In regards to "different physico-chemical properties" physico-chemical properties have no bearing on reason to modify. Furthermore, as Applicant indicates, Factor VIII has MW of 330,000; prothrombin has MW of 72,000. Factor X has MW of 58,500. Factor V has MW of 330,000; Factor VIIa has MW of 50,0000. For example, Factor X is a protein having 482 amino acids; Factor VIII is a protein having 2319 amino acids; Factor V is a protein having 2206 amino acids. Given the different size and sequence of each of coagulation factors taught in Baru, one would expect these to have different physiochemical properties from one another. Yet, Baru reference teaches that different sized proteins can bind externally to the colloidal particle, and the half-life of the protein is extended. Given the variation of protein sizes taught by Baru reference, any size protein would work; size is not relevant. Further, Factor VIIa has close MW to Factor X. One would expect Factor VIIa to have the same effect as Factor X. In regards to "Martin reference teaches away from using cholesterol," Martin teaches that other lipid components, such as cholesterol, are also known to contribute to membrane rigidity and

stability in lipid bilayer structures. Therefore, one would be motivated to add the cholesterol to increase the stability in lipid bilayer structures. Therefore, Martin reference does not teach away from using cholesterol.

Furthermore, Heldman et al teach amphiphilic compound capable of forming vesicles or liposomes. The reference teaches that the vesicle preparations are designed for delivering therapeutic agents which have a short lifetime at the delivery sites (e.g. stomach, intestine, etc) and have to be released at the site of action in another part of the body...insulin for the treatment of diabetes, or Cop 1 (Copaxone®) for the treatment of multiple sclerosis, or antibodies such as Herceptin for the treatment of breast cancer (see paragraph [0224], and claims 39-40). Both Martin and Heldman references teach entrapment of therapeutic agents in vesicles or liposomes. Baru, Martin and Heldman references all teach the utilization of colloidal particles and liposomes to increase the half-lives of therapeutic agents. Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life *in vivo***, because they are not removed by the RES.

Braxton patent No. '897 teaches exemplary proteins for which an increase half-life has been accomplished by PEGylation of the protein include: hGH, **insulin**, interferon, tPA, **EPO, G-CSF…factor VIII…IgG** and so on.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al, Martins et al patents, Heldman et al and Braxton patent, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and

substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru and Martin, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V and Martin et al teach Interferon gamma, G-CSF, GM-CSF, and other protein that are incorporated with the liposomes. Since entrapped within colloidal particle (Martin and Heldman) worked, and one worked for binding externally to the colloidal particle (Baru), one would expect that both would work the same way. Therefore, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. One of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes

can be used which **have a longer half-life *in vivo***, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated in vivo without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide. Since COPAXONE® has short half-life, one would expect that by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used to increase the half life *in vivo*.

15. Claims 28-34, 36-42, 54, 57-60, 62-65, 67-69, 71-74 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Braxton (US Patent No. 5,766,897) and Papatheodoridis et al (Journal of Hepatology, 1999, 31: 747-750).

The teachings of Baru and Martin et al are described, *supra*. Baru further teaches a method of treating a patient suffering fro hemophilia comprising administering to said patient a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of coagulation factor VIII (FVIII) not encapsulated in colloidal particle. The difference between the reference and the instant claims is that the reference does not teach factor VIIa.

However, Braxton patent No. '897 teaches exemplary proteins for which an increase half-life has been accomplished by PEGylation of the protein include: hGH, **insulin**, **interferon**, tPA, **EPO, G-CSF…factor VIII…**IgG…**superoxide dimutase** and so on (see column 25, lines 9-38). Papatheodoridis et al further teaches that factor VII has the shortest half life (see p. 747, right column).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al, Martins et al patents, Braxton patent and Papatheodoridis reference, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Baru further teaches a method of treating hemophilia comprising administering a pharmaceutical composition comprising FVIII not encapsulated in colloidal particle.

Martin et al teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes, which have short half-life.

Furthermore, Braxton reference teaches proteins for which an increase half-life has been accomplished by PEGylation of the protein include: hGH, **insulin**, **interferon**, tPA, **EPO, G-CSF…factor VIII…**IgG…**superoxide dimutase** and so on (see column 25, lines 9-38). Papatheodoridis et al further teaches that factor VII has the shortest half life (see p. 747, right column). Further, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life *in vivo***, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated *in vivo* without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). PEGylation of proteins increases half-life of these proteins, including G-CSF, interferon gamma and factor VIII (including prothrombin, factor X and so on disclosed in Baru reference), insulin, EPO, factor VIII and antibodies (Braxton). Since Factor VII is known to have the shortest half-life, one of ordinary skill in the art would have been motivated to increase

the half-life of a therapeutic compound known to have the shortest half-life. There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide. Additionally, factor VIIa is in the same family of compounds as Factor VIII. Therefore, one would expect that factor VIIa would at least work the same as Factor VIII.

Response to Applicant's Arguments

16. Applicant argues that "a proper case of prima facie obviousness has not been established because the combination of Baru with Martin is improper because there is no suggestion or motivation to combine the reference teachings or to modify the reference." Applicant further argues that "the proteins or polypeptides of Baru are not encapsulated in the colloidal particles. Martin, on the other hand, describes liposome compositions which 'contain the therapeutic compound in liposome-entrapped form'. The skilled artisan would not combine these references since they teach liposome compositions of significantly different structure, one in which the protein is outside the liposome and one in which the protein is inside the liposome...the skilled artisan when

reviewing Martin that describes encapsulate proteins, would have not motivation to look to art describing liposomes where the protein is not encapsulated." Applicant further argues that "although Baru discloses the coagulation factors Factor VIII, prothrombin, Factor X and Factor V, this does not make obvious the use of Factor VIIa...these factors have completely different physico-chemical properties. It is these properties, and not the therapeutic use, which determine whether the protein will be active when bound to the colloidal particle, and whether the half life will be extended." Applicant further argues that "Martin teaches away from using cholesterol." Furthermore, Applicant argues that "Braxton describes that PEGylation of certain proteins increases their half lives. Braxton does not teach or allude to the presently claimed composition." Further, Applicant argues that "Papatheodoridis is merely cited as teaching that Factor VII has a short half life. However, Factor VII is not Factor VIIa. FVII is a single-chain protein. Once bound to Tissue Factor, FVII is activated to FVIIa by different proteases. FVIIa consists of two chains linked via a single disulfide bond."

17. Applicant's arguments have been fully considered but have not been found persuasive. Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles. Additionally, Baru teaches that these formulations extend the half-life of proteins and the reference teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, binds to membranes comprising phosphatidylcholine:phosphatidylserine (PC:PS) (i.e., two amphipathic lipids); non-

limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al teach a liposome composition for extended release of a therapeutic compound in to the bloodstream. Martin reference teaches that the liposomes are composed of vesicle forming lipids (phospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylinositol (PI) and the like) and further teaches that the liposomes are between 1-20 mole percent of vesicle-forming lipid derivatized with hydrophilic polymer, having sizes in a selected size range between 0.1 and 0.4 microns, and contain the therapeutic compound in liposome-entrapped form. The mere fact that one is entrapped would not negate the reasonable expectation of success. Baru reference showed that proteins or polypeptide externally binding the colloidal particles, and Martin reference showed that protein or polypeptides encompassed within the same colloidal particle. Both references teach that the half-life of the protein or polypeptides can be extended. Furthermore, Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life *in vivo***, because they are not removed by the RES.

In regards to Applicant's argument that "although Baru discloses the coagulation factors Factor VIII, prothrombin, Factor X and Factor V, this does not make obvious the use of Factor VIIa...these factors have completely different physico-chemical properties," Baru teaches the same family of proteins, coagulation factors Factor VIII, prothrombin, Factor X and Factor V. It would have been obvious to one of ordinary skill in the art to substitute equivalent protein Factor VIIa known as coagulation factor for

Factor VIII, prothrombin, Factor X and Factor V. In regards to "different physico-chemical properties" physico-chemical properties have no bearing on reason to modify. Furthermore, as Applicant indicates, Factor VIII has MW of 330,000; prothrombin has MW of 72,000. Factor X has MW of 58,500. Factor V has MW of 330,000; Factor VIIa has MW of 50,0000. For example, Factor X is a protein having 482 amino acids; Factor VIII is a protein having 2319 amino acids; Factor V is a protein having 2206 amino acids. Given the different size and sequence of each of coagulation factors taught in Baru, one would expect these to have different physiochemical properties from one another. Yet, Baru reference teaches that different sized proteins can bind externally to the colloidal particle, and the half-life of the protein is extended. Given the variation of protein sizes taught by Baru reference, any size protein would work; size is not relevant. Further, Factor VIIa has close MW to Factor X. One would expect Factor VIIa to have the same effect as Factor X. In regards to "Martin reference teaches away from using cholesterol," Martin teaches that other lipid components, such as cholesterol, are also known to contribute to membrane rigidity and stability in lipid bilayer structures. Therefore, one would be motivated to add the cholesterol to increase the stability in lipid bilayer structures. Therefore, Martin reference does not teach away from using cholesterol.

In regards to "Factor VII is not Factor VIIa," it is well known in the art that Factor VII converts to Factor VIIa, that one of ordinary skill in the art would have expected that Factor VIIa would also have short half life. Additionally, Papatheodoridis teaches that administration of rFVIIa to correct the prolonged prothrombin time (PT) (see p. 747, right

column, bottom). Furthermore, Papatheodoridis teaches that Factor VII plays a key role in the initiation of the coagulation cascade, and its deficiency is readily reflected by prolongation of PT...it is expected that administration of rFVIIa will correct the prolonged PT in cirrhotic patients with factor VII deficiency (see p. 749, left column, bottom). Papatheodoridis reference teaches the use of FVIIa to correct factor VII deficiency. Therefore, one would expect that FVII and rFVIIa would function the same.

Braxton patent No. '897 teaches exemplary proteins for which an increase half-life has been accomplished by PEGylation of the protein include: hGH, **insulin**, interferon, tPA, **EPO, G-CSF…factor VIII…IgG** and so on.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al, Martins et al patents, Braxton patent and Papatheodoridis et al, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru and Martin, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount

of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V and Martin et al teach Interferon gamma, G-CSF, GM-CSF, and other protein that are incorporated with the liposomes. Since one worked with entrapped within colloidal particle (Martin), and one worked for binding externally to the colloidal particle (Baru), one would expect that both would work the same way. Therefore, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. One of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life *in vivo***, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated in vivo without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used

which have a longer half-life *in vivo*. There is a reasonable expectation that other coagulation factor proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

18. Claims 35, 61 and 66 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Ishikawa et al (US Patent No. 5,824,778) and Igari et al (US Patent No. 5,534,269) as applied to claims 28-34, 36-42, 57, 59-60, 62-65, 67-68, 73-74 above, and further in view of Zalipsky S (US Patent No. 6,586,001).

The teachings of Baru and Martin et al, Ishikawa et al and Igari et al are described, *supra.* The difference between the references and the instant claims is that the reference does not teach aminopropanediol distearoyl (DS).

However, Zalipsky teaches liposomes containing PEG-substituted neutral lipopolymers provide similar circulation times to liposomes incorporating conventional, negatively charged PEG-substituted phopholipids. Further, the reference teaches that use of the uncharged lipopolymers can also present advantages in terms of interactions with cell surface and reduce leakage of charged substances (see abstract). The reference teaches different types of lipids (see Col. 3, lines 1-24) and the synthesis of PEG-Aminopropanediol distearoyl (see Example 1A).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings, since all of the protein therapeutics have short half-lives. Zalipsky teaches liposome containing PEG-substituted neutral lipopolymers containing proteins, antibodies, vitamins and so on, and the PEG-DS lipopolymer. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings, teach a need to increase the half-life of the therapeutic proteins, and therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which have a longer half-life in vivo, because they are not removed by the RES (see p. 4, lines 1-6). Therefore, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. Martin reference teaches that these PEG-neutral liposomes are well tolerated in vivo without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. Both Ishikawa et al and Igari et al teach that "it has been desired to prolong the half-life of human G-CSF in the body as to enhance it s effects, as may be expected…interferons (alpha, beta, gamma)...erythropoietin and granulocyte colony-stimulating factor (G-CSF). These proteins, however, since they have generally short biological half-life, must be administered frequently, posing the significant physical burden of injection on patients. Zalipsky teaches that the neutral lipopolymers provide advantages in terms of interactions with cell surfaces. Since Baru teaches DSPE-PEG lipopolymer was successful and Zalipsky teaches PEG-DS lipopolymer was successful,

one of ordinary skill in the art would have been motivated to try DS, since DS and DSPE belong to the same family, and expect that DS would be successful. Furthermore, pegylation of protein is general concept in the protein arts. There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life in vivo. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

Response to Applicant's Arguments

19. Applicant argues that "claims 35, 61 and 66 have been cancelled without prejudice or disclaimer. Accordingly, this rejection is moot with regard to claims 35, 61 and 66."

20. Applicant's arguments have been fully considered but have not been found persuasive. Amendment to claims filed on December 28, 2009 does not indicate that claims 35, 61 and 66 have been cancelled. Claims 35, 61 and 66 have the status identifier "previously presented". Therefore, the rejection as stated on the record is maintained.

21. Claim 70 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Braxton (US Patent No. 5,766,897) and Papatheodoridis et al (Journal of Hepatology, 1999, 31: 747-750) as applied to claims 28-34, 36-42, 45, 54, 57-60, 62-65, 67-69, 71-74 above, and further in view of Zalipsky S (US Patent No. 6,586,001).

The teachings of Baru, Martin et al, Braxton and Papatheodoridis et al are described, *supra*. The difference between the reference and the instant claim is that the reference does not teach aminopropanediol distearoyl (DS).

However, Zalipsky teaches liposomes containing PEG-substituted neutral lipopolymers provide similar circulation times to liposomes incorporating conventional, negatively charged PEG-substituted phopholipids. Further, the reference teaches that use of the uncharged lipopolymers can also present advantages in terms of interactions with cell surface and reduce leakage of charged substances (see abstract). The reference teaches different types of lipids (see Col. 3, lines 1-24) and the synthesis of PEG-Aminopropanediol distearoyl (see Example 1A).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al, Martins et al patents, Braxton patent and Papatheodoridis reference, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term “proteins or polypeptides capable of externally binding said colloidal particles” includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such

proteins are coagulation factors such as prothrombin, Factor X and Factor V. Baru further teaches a method of treating hemophilia comprising administering a pharmaceutical composition comprising FVIII not encapsulated in colloidal particle. Martin et al teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes, which have short half-life. Furthermore, Braxton reference teaches proteins for which an increase half-life has been accomplished by PEGylation of the protein include: hGH, **insulin**, **interferon**, tPA, **EPO, G-CSF…factor VIII…**IgG…**superoxide dimutase** and so on (see column 25, lines 9-38). Papatheodoridis et al further teaches that factor VII has the shortest half life (see p. 747, right column). Further, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life in vivo**, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated *in vivo* without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). PEGylation of proteins increases half-life of these proteins, including G-CSF, interferon gamma and factor VIII (including

prothrombin, factor X and so on disclosed in Baru reference), insulin, EPO, factor VIII and antibodies (Braxton). Since Factor VII is known to have the shortest half-life, one of ordinary skill in the art would have been motivated to increase the half-life of a therapeutic compound known to have the shortest half-life. Zalipsky teaches liposome containing PEG-substituted neutral lipopolymers containing proteins, antibodies, vitamins and so on, and the PEG-DS lipopolymer. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts teach a need to increase the half-life of the therapeutic proteins, and therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which have a longer half-life in vivo, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated in vivo without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. Zalipsky teaches that the neutral lipopolymers provide advantages in terms of interactions with cell surfaces. Since Baru teaches DSPE-PEG lipopolymer was successful and Zalipsky teaches PEG-DS lipopolymer was successful, one of ordinary skill in the art would have been motivated to try DS, since DS and DSPE belong to the same family, and expect that DS would be successful. Furthermore, pegylation of protein is general concept in the protein arts. There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not

encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life in vivo. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide. There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. Additionally, factor VIIa is in the same family of compounds as Factor VIII. Therefore, one would expect that factor VIIa would at least work the same as Factor VIII.

Response to Applicant's Arguments

22. Applicant argues that "claim 70 has been cancelled without prejudice or disclaimer. Accordingly, this rejection is moot with regard to claim 70."

23. Applicant's arguments have been fully considered but have not been found persuasive. Amendment to claims filed on December 28, 2009 does not indicate that claims 35, 61 and 66 have been cancelled. Claim 70 has the status identifier "previously presented". Therefore, the rejection as stated on the record is maintained.

Conclusion

24. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654